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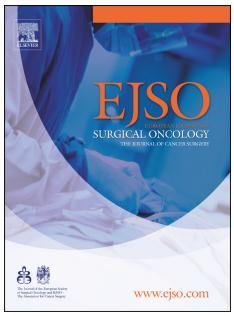

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Original article

Neoadjuvant chemoradiation and pancreaticoduodenectomy for initially locally advanced head pancreatic adenocarcinoma

O. Turrini MD[*], F. Viret MD[**], L. Moureau MD°, J. Guiramand MD[*], V. Moutardier MD[*], B. Lelong MD[*], M. Giovannini MD[***] and JR. Delpero MD[*]

Departments of [*]Surgical Oncology, [**]Medical Oncology, [***]Endoscopy and °Radiotherapy Institut Paoli-Calmettes and Université de la Méditerranée Marseille, France.

Corresponding author: Olivier Turrini
Institut Paoli-Calmettes
232 Bd de Sainte Marguerite
13009 Marseille, France.
Telephone number: 0491223660
Fax number: 0491223550
Email address: oturrini@yahoo.fr
turrinio@marseille.fnclcc.fr

Abstract

BACKGROUND: The most accepted treatment for locally advanced pancreatic adenocarcinoma (LAPA) is chemoradiotherapy (CRT). We sought to determine the benefit of pancreaticoduodenectomy (PD) in patients with LAPA initially treated by neoadjuvant CRT.

METHODS: From January 1996 to December 2006, 64 patients with LAPA (borderline, n=49; unresectable, n=15) received 5-fluorouracil-cisplatin-based CRT. Of the 64 patients, 47 had progressive disease at restaging. Laparotomy was performed for 17 patients, and PD was performed in 9 patients (*resected* group). Fifty-five patients had CRT followed by gemcitabine-based chemotherapy (*unresected* group).

RESULTS: The median survival and overall 5-years survival duration of all 64 patients were 14 months and 12%, respectively. The mean delay between diagnosis and surgical resection was 5.5 months. Mortality and morbidity from PD were 0% and 33%, respectively. The median survival of the *resected* group versus the *unresected* group was 24 months vs. 13 months. Three specimens presented a major pathological response at histological examination. No involved margins were found and positive lymph nodes were found in one patient. Resected patients developed distant metastases.

CONCLUSIONS: PD after CRT was safe and resected patients had interesting survival rates. However, resected patients developed metastatic disease and new neoadjuvant regimens are needed to improve the survival of these patients.

Key words: pancreatic adenocarcinoma, locally advanced, neoadjuvant, chemoradiation

Introduction

Resection and perioperative treatment for patients with resectable pancreatic adenocarcinoma has improved survival over the last two decades but overall patient survival remains poor[1,2]. At the time of diagnosis, tumors are classified according to radiological findings: the improvement of helical dual phase scanning sensitivity and surgeons' experience has advanced the classification from resectable and unresectable to resectable, borderline and unresectable[3,4]. Locally advanced pancreatic adenocarcinoma (LAPA), comprising both borderline and unresectable tumors, is characterized by the abutment or invasion of major vascular structures preventing surgeons from achieving optimal R0 resection. Thus, patients diagnosed with LAPA are likely to be spared from surgery; rapid disease progression and poor clinical status means patients undergo exclusively medical treatment with poor survival rates[5,6]. However, patients diagnosed with non-metastatic LAPA with a good clinical status are likely to undergo chemoradiation (CRT)[7]. Although it is impossible for patients with arterial adhesion/invasion to undergo resection, venous involvement proved not to be a contraindication to resection[8-13]. Thus, despite low resection rates, several reports showed interesting results on overall survival[14-20] after pancreaticoduodenectomy (PD) for LAPA. Moreover, not resecting the tumor exposed patients to recurrent biliary and digestive obstruction, increasing the incidence of uncontrollable pain and a poor quality of life[21]. In 1996, we started a neoadjuvant approach for pancreatic adenocarcinoma and we sought to determine the impact of PD after CRT in patients initially diagnosed with LAPA.

Methods

Patient selection

Between January 1996 and December 2006, 151 patients were diagnosed with a histologically proven non-metastatic adenocarcinoma of the pancreatic head and were considered eligible for neoadjuvant CRT. Pancreatic cancer was staged by physical examination, chest radiography, biopsy (fine needle aspiration with Wilson-Cook 22 gauge, 8cm needles) obtained by endoscopy under ultrasound guidance (EUS) (Pentax-Hitachi, Hamburg, Germany), and thin-section contrast-enhanced helical dual phase scanning (CT scan). Patients with adenocarcinoma of the tail or neck of the pancreas, intraductal papillary mucinous adenocarcinoma, tumors of neuroendocrine origin or with carcinoma of the duodenum, distal common bile duct, or ampulla of Vater were excluded from this study. Patients having any major comorbidity precluding consideration of pancreatic surgery were also excluded. Resectability was assessed by both surgeons and radiologists and tumors were classified as resectable (n=87), borderline (n=49) and unresectable (n=15) (table 1). Biliary stenting by a 10-French plastic stent was performed before or during neoadjuvant CRT if any sign of cholangitis or complete biliary obstruction occurred.

Primary treatment and restaging (n=64)

Neoadjuvant CRT consisted of standard-fractionation radiotherapy (45 Gy for 5 weeks) combined with concurrent chemotherapy, including continuous infusion of 5-fluorouracil (650 mg/m^2 on Days 1–5 and Days 21–25) accompanied by a cisplatin bolus (80 mg/d/m^2 on Days 2 and 22). World Health Organization (WHO) Grades 2, 3 or 4 toxicity events were recorded during CRT and 4 patients (6%) experienced grade 3 toxicity. All patients were restaged after completion of chemoradiation and radiologic tumor response was determined using Response Evaluation Criteria In Solid Tumors (RECIT) criteria for staging. Forty six patients had progressive disease (metastases, n=25; increase in gross tumor size, n=12; carcinomatosis, n=9. The serum level of CA19-9 was not retained to spare patients from explorative laparotomy if no distant metastasis was detected at restaging. The laparoscopic approach was routinely performed and one patient was identified with carcinomatosis.

Explorative laparotomy (n=17)

Laparoscopic evaluation of vascular involvement using echolaparoscopy was not used routinely because: a) CRT and/or the presence of metallic biliary stents made it difficult to achieve an appropriate analysis of the tumor boundaries, b) endosonographic encasement did not allow for diagnosis of the real features of the involvement (post-radic or tumoral), and c) biopsy under echolaparoscopy of perivascular tissue was hazardous if needed. During laparotomy, 4 explorative steps were always carried out. ***Step one***: careful examination of the entire abdomen using a laparoscopic approach. ***Step two***: dissection of the superior mesenteric artery (SMA) on its left side, pulling down the duodenojejunal angle. The SMA was then completely dissected on both face and multiples biopsies were performed to prevent any tumoral adhesion and R1/R2 resection. This allowed for a complete lymph node resection if required (SMA lymphadenectomy). ***Step tree***: dissection of the inferior side of the pancreas, including entire dissection of the portal vein (PV) and the superior mesenteric portal vein (SMPV) confluent. ***Step four:*** dissection of the upper side of the pancreas to identify encasement of the hepatic artery (HA) or celiac trunk CT. This allowed for the complete resection of the lymph nodes of the corresponding area. Multiple perivascular biopsies were routinely performed to distinguish post-radic tissue with tumor involvement. No false positive or negative results were noted after frozen section analyses. Patients underwent a resection with the intention of a cure if the biopsies were negative.

Resection (n=9)

Nine patients (*resected* group) had a PD with extended lymphadenectomy. Two patients needed an enlarged resection adjacent to nearby organs (right colon, n=2). We routinely performed staining of the pancreatic section, posterior margin and PV bed margin in the operating room. Pathological examination included the margin status, lymph node involvement, gross tumor size and perineural invasion. The absence of residual cancer in the resected specimen (sterilized specimen) after CRT was defined as a complete pathological response (ypT0). Minimal residual disease was defined by presence of tumor < 2mm in the resected specimen. No resected patients had adjuvant chemotherapy. Fifty-five patients (*unresected* group) had CRT followed by systemic gemcitabine-based chemotherapy for an unresectable tumor.

Follow-up and statistical analysis

All living patients were evaluated by a combined medical and surgical team at 1, 4 and 6 months post-operatively, and every year thereafter. Physical examination, thin-section contrast-enhanced helical dual phase CT scan and tumor markers (CEA, CA 19-9) were routinely obtained in follow-up. The type of recurrence was noted (metastasis, carcinomatosis or local recurrences). Survival was measured from the date of diagnosis to the date of death or January 1, 2008, the censor date. Survival was examined using the Kaplan-Meier method. Statistical comparisons were conducted using log rank tests; $p<0.05$ was considered to be statistically significant.

Results

Entire population, restaging (n=64)

No patients were lost to follow-up, with a mean follow-up of 38 months (range 12-117). Overall 1, 3 and 5 years survival of all 64 patients who underwent primary treatment and restaging were 58%, 12% and 12%, respectively; the median overall survival was 14 months. The mean delay between diagnosis and surgical resection was 5.5 months (range 3-8). In patients without distant disease found at restaging (n=34), local tumor progression was documented in 12 patients, stable disease was documented in 16 patients, and partial remission was documented in one patient.

Patients who underwent explorative laparotomy (n=17) and resected patients (n=9)

The characteristics of patients having an explorative laparotomy are summarized in Table 2. Pathological findings and outcomes of resected patients (n=9) are summarized in Table 3. Mortality and morbidity were 0% and 33% (gastric emptying, n=2; pancreatic fistula, n=1), respectively. Overall 1 and 3 years survival rates of the *resected* group versus the *unresected* group were 78% vs. 53% (p=0.04) and 65% vs. 3% (p<0.01), respectively. The median survival of the *resected* group vs. the *unresected* group was 24 months vs. 13 months (figure 1), respectively.

Pathological findings (table 3)

Three patients had a sterilized (ypT0, n=1) or minimal residual disease (n=2) at histological examination. No involved margins were found. Positive lymph nodes were found in 1 patient.

Recurrences (table 3)

Four patients of the *resected* group developed distant metastatic recurrence. Four patients were alive without recurrence with a mean follow up of 32 months. One patient died of another cause (myocardial infarction) than pancreatic cancer during follow up.

Discussion

Using strict CT-scan criteria to evaluate LAPA, complete resection was achieved in only 14% of patients. However, the overall survival time seemed to be improved due to the local effect of CRT (no margin involved, downstaging of tumors) and time-selection sparing patients with progressive disease.

Resection rate

Resection rates vary from 13% to 63% in the literature (table 4) due to a) CT-scan and endoscopic criteria chosen to define LAPA and/or b) the fact that studies focus on borderline tumors. Arterial involvement remains a contraindication for resection due to the high morbidity involved and low benefit gained with regards to survival. On the other hand, several reports[8-13] showed that resection/reconstruction of the PV or SMPV confluent were safe and improved survival. Therefore, tumors in contact with major venous vasculature without circumferential encasement, PV thrombosis or large involvement of the SMPV confluent must be considered resectable tumors. Those findings help to optimize the resectability classification: pancreatic head adenocarcinoma could be staged as resectable, borderline or unresectable. However, the total encasement of the SMA or CT (previously an unresectable tumor) was associated with a poor resection rate compared to a case of tumor abutment (previously classified as a borderline tumor) (7% versus 16%, respectively).

Survival

The median survival of patients with LAPA was poor (14 months) as reported in table 4. However, patients with LAPA who underwent curative PD had comparable median survival times than patients with initially resectable tumors[22]. However, there were two major criticisms of our study. Firstly, the mean delay between diagnosis and surgery was over 5 months, higher than we reported[23] for patients with initially resectable tumors. In the early experience of the series, the persistence of periarterial thickness at restaging was concerning and patients underwent a supplementary observation time before undergoing a laparotomy. In 2005, Sa Cuhna et al[24] showed that the thickness around SMA or celiac axis could be treated by CRT and did not preclude a laparotomy. Thus, we scheduled surgery 5 weeks after completion of CRT, as for neoadjuvant CRT for resectable tumors. We supposed that our additional time-selection of CRT participated to spare patients with disease progression and identified good candidates for surgery. Secondly, the small number of patients in the *resected* group precluded from emphatic conclusions. Nevertheless, our findings seem to be comparable to other series and we found that patients who underwent PD for LAPA did have an improved survival time.

Future strategies

CRT associated with PD enabled the optimal local control of the disease, as confirmed by tumor downstaging (one patient with ypT0 stage tumor and 2 patients with minimal residual disease), margin free resections and no identified local recurrences[25-28]. However, outstanding local control did not prevent distant recurrences and 4 resected patients experienced metastatic spread. On the other hand, 53% of patients with initially diagnosed localized disease developed metastasis during CRT and consequently underwent inappropriate local treatment. We strongly advocate that systemic chemotherapy should be used in the management of patients diagnosed with apparently non-metastatic LAPA. We suggest that a neoadjuvant approach should be preferred and should include gemcitabine-based chemotherapy and radiation therapy. This makes sense, particularly since delayed recovery after surgery precludes adjuvant therapy in approximately 30% of patients who undergo elective PD as the initial treatment for pancreatic adenocarcinoma[29,30]. However, the best neoadjuvant regimen is still to be determined[31]. Recently, new neoadjuvant strategies have shown interesting results in resectable and locally advanced pancreatic cancer[32]. However, further studies are needed to determine the impact on the postoperative course and overall survival in resected patients with initially diagnosed LAPA.

Conclusions

Patients with pancreatic cancer should be discussed within a multidisciplinary staff setting to determine tumor resectability and decide on appropriate neoadjuvant treatment (drugs, doses, sequences and so on). Patients who underwent curative resection had comparable survival to patients with an initially resectable tumor. Thus, despite low resection rates, the opportunity for curative resection should not be refuted based on a CT-scan assessment. While waiting for more effective therapies besides gemcitabine and 5-FU, new neoadjuvant regimens have to be assessed in order to increase arguments for surgery as a last approach.

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 2: characteristics of patients who underwent explorative laparotomy (n=17).

Mean age (yo)	56 (range 37-70)
Tumor size	3.4 (range 2.8-4.2)
Ca19-9 levels (IU/ml)°	122.8 (range 2-423)
Initial cause of LAPA classified	
PV / SMPV confluent involvement	12
SMA / CA / HA involvement	7
Delay diagnosis / surgery (months)	5.5 (range 3-8)
Resected	9
Tumor size (cm)	3.2 (3-3.9)
Ca19-9 levels (IU/ml)°	95.5 (range 8-253)
Operative duration (mn)	447 (range 365-510)
Blood loss (mL)	220 (range 50-720)
Cause of non resection	
Arterial encasement	3
Venous encasement	5

(**PV**: Portal Vein
SMPV: Superior Mesenterico Portal Vein
CA: Celiac Axis
SMA: Superior Mesenteric Artery
HA: Hepatic Artery)
(°CA 19-9 levels were measured at time of diagnosis / after correction of obstructive jaundice)

Table 3: characteristics of patients with LAPA who underwent pancreaticoduodenectomy.

Patient	1	2	3	4	5	6	7	8	9
Age	63	56	68	59	59	58	43	59	67
Vessel involved	PV	PV	CA	PV+SMA	PV	PV	SMA+CA	PV+SMA	PV
Delay to surgery (months)	3	5	7	3	6	5	8	5	8
CA 19-9 levels (IU/ml)°	15	110	253	185	8	29	139	14	89
Vascular resection	L. PV	L. PV	no	no	T. PV	no	no	L. PV	L.PV
Operative duration (mn)	421	382	365	485	510	390	505	490	475
Blood loss (ml)	150	120	50	380	720	120	80	210	160
Specimen status	-	-	-	-	-	MRD	MRD	-	Sterilized
Nodes (positive/total)	0/11	0/9	0/17	0/6	**1/5**	0/18	0/5	0/7	0/10
Positives margins	no	no	no	no	no	no	no	no	no
Perineural invasion	no	yes	yes	yes	yes	no	no	yes	no
Recurrence	**-***	Meta**.***	-	Meta**.***	-	-	Meta.*	Meta.	-
Morbidity	no	no	PF	no	no	GE	no	GE	no
Survival (months)	4	12	-	13	-	-	27	-	-

(**PV**: Portal Vein;
CA: Celiac Axis
SMA: Superior Mesenteric Artery
L. PV: Lateral resection of portal vein
T. PV: Troncular resection of portal vein
MRD: Minimal Residual Disease
PF: Pancreatic Fistula
GE: Gastric Emprtying
*: patient dead)
(°CA 19-9 levels were measured at time of diagnosis / after correction of obstructive jaundice)

Table 4: patients receiving neoadjuvant CRT for LAPA.

	year	n	Chemo.	Resection rate	Median survival resected (months)	Median survival unresected (months)
***Wanebo *et al.*[14]**	2000	14	5 FU/cisplat	63%	19	-
***Mehta *et al.*[15]**	2001	15	5 FU	60%	30	8
Ammori *et al.*[16]	2003	67	Gem	13%	17.6	11.9
Aristu *et al.*[17]	2003	47	5FU/ cisplat	19%	23	10
Massuco *et al.*[18]	2006	23	Gem	26%	20	12
Lind et *al.*[19]	2006	17	Ox/cap	47%	29	-
***Katz *et al.*[20]**	2008	160	Gem	41%	40	13
Current series	2008	64	5 FU/cisplat	14%	24	13

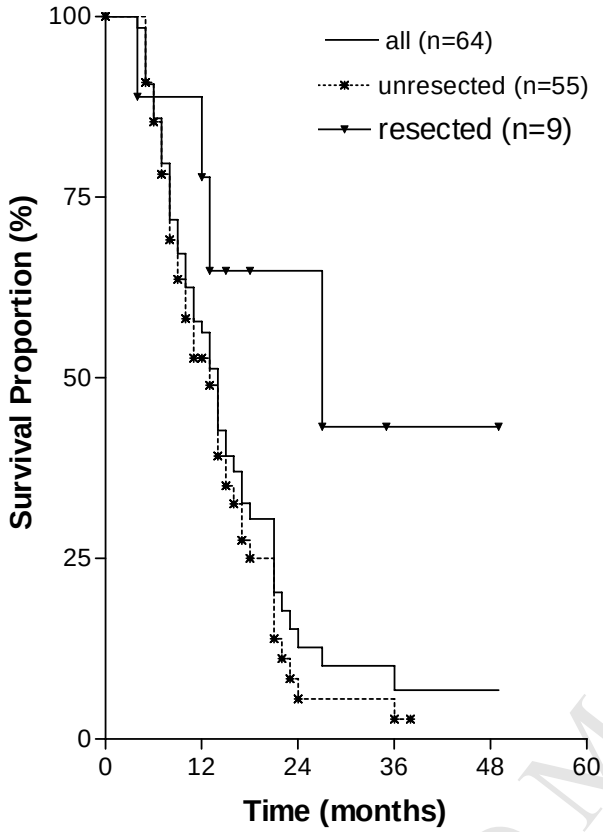
(*borderline series; **Gem**: gemcitabine-based chemoradiation; **cisplat**: cisplatin-based chemoradiation; **ox**: oxaliplatin; **cap**: capecitabine)

Table 1: allocation of patients with locally advanced pancreatic adenocarcinoma according to radiological findings.

	Borderline (n=49)	Unresectable (n=15)
SMA	Tumor abutment ≤ 180° of the circumference	Encased > 180°
CT / HA	Short segment encasement / abutment	Encased with extension to the CA origin
SMV / PV	Short segment occlusion	Occluded and no technical option for reconstruction

(**SMA:** Superior Mesenteric Artery; **CT**: celiac trunk; **HA**: Hepatic Artery; **SMV:** Superior Mesenteric Vein; **PV:** Portal Vein)

Figure 1: overall survival of patients with Locally Advanced Pancreatic Adenocarcinoma (LAPA).



Log –rank test unresected vs. resected = ***0.01***

Subjects at risk

	0	**12**	**24**	**36**	**48**
all patients	64	37	6	3	2
unresected	55	29	3		
resected	9	8	4	2	1